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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	15

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,704	DEDHAR ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *2,3,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Amendment filed June 27, 2003 in Paper No. 14.

Claims 1-18 are pending in the instant application. Claims 1 and 10 have been amended. Claims 2, 3, 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Response to Amendment

Priority

The updated reference to priority in the first line of the Specification is acknowledged.

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 4, 5-10 and 13-18 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is withdrawn in view of Applicants arguments that the term "integrin-linked kinase" is an art-recognized term.

Claims 1, 4, 5-10 and 13-18 were rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for the reasons of record set forth in the previous Office Action, filed March 27, 2003.

Applicants argue that the presently claimed invention is enabled, and could be practiced by one of ordinary skill in the art without undue experimentation. More specifically, Applicants argue that the non-specific activity of wortmannin and LY294002 is not indicative that the compounds are not useful clinical entities. Applicants rely on Drevs et al., 2003. Applicants further argue that several issued US patents have disclosed ILK-specific inhibitors. Applicants rely on US Patent Nos. 6,214,813; 6,436,914; and 6,420,040. Applicants also argue that the use of IEC-18 as an *in vitro* model for testing anti-inflammatory potential for ILK inhibitors is rationale. Applicants rely on Sutherland et al., 1994, Waterhouse and Stadnyk, 1999, US Patent Application 20020155179 and Dedhar et al., 2002. Applicants also argue that ILK inhibitors are useful *in vivo*. Applicants rely on Hu et al., 2002. Applicants contend that a considerable amount of experimentation is permissible, if it is merely routine. Applicants rely on *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) and MPEP §2164.01. Applicants further contend that compliance with the enablement requirement does not require or mandate that a specific example be disclosed. Applicants further argue that the amount of experimentation required to inhibit or prevent inflammation using compounds that specifically inhibit integrin-linked kinase would not be undue because (a) examples of inhibitors are provided, (b) guidance is given on how to screen for additional inhibitors, and (c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the optimal dosage.

Applicants arguments have been fully considered, but are not found persuasive because the weighing of several factors as set forth in *Wands* was the standard applied under 35 USC 112, first paragraph rejections in the previous Official Action. Working examples are, of course, not an absolute requirement for enablement, but are a legitimate factor in determining lack of enablement. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). The need for additional experimentation, as in routine screening, is not an absolute bar to enablement, as long as the required experimentation is not undue. However, because of the lack of predictability of the art, as demonstrated by the assertion by Stein, RC that the lack of selectivity among wortmannin and LY294002, together with the instability of wortmannin and the insolubility of LY294002, means that neither has very promising pharmaceutical potential, and the specification lack of particular guidance or particular direction, undue experimentation would be required of one of skill in the art to make and use the claimed invention. Further regarding the lack of predictability of the art, a very recent published article by Wymann et al. (Trends in Pharmacological Sciences, 2003 Vol. 24:366-376) disclose that although wortmannin has been identified as an anti-inflammatory substance, wortmannin proved to be toxic to rats after given orally (see page 373, last paragraph). Given the unpredictability in the art of using wortmannin and LY294002 *in vivo*, due to their known instability, insolubility and toxicity, it would require more than routine experimentation to make and use the claimed invention.

Regarding Applicants arguments that issued US patents have disclosed ILK-specific inhibitors, these US patents have not described how the skilled artisan would use ILK-specific inhibitors *in vivo,* as contemplated in the instant invention. Regarding Applicants arguments that non-specific activity is not indicative that a compound is not useful clinical entities, Applicants

example that multitarget tyrosine kinase inhibitor compounds have been used in clinical trails is irrelevant to the instant invention. The feasibility of a multitarget tyrosine kinase inhibitor does not demonstrate the feasibility of an ILK-specific inhibitor of a wholly different structure, as is the instant case. Regarding Applicants arguments that LY294002 is useful *in vivo*, Hu et al. (Cancer Research, 2002 Vol. 62:1087-1092) assert that LY294002 decreases growth of ovarian carcinoma and ascites formation in an athymic mouse xenogeneic transplant model of ovarian cancer, however, the dose of LY294002 used to decrease tumor growth resulted in significant dermatological toxicity (see Abstract). Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art, at the time of the invention, would have required an undue amount of experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 102

Claims 1, 4, 5, 6, 7, 10, 13, 14, 15 and 16 were rejected under 35 U.S.C. 102(b) as being anticipated by Norman et al. (Journal of Medicinal Chemistry, 1996 Vol. 39:1106-1111). This rejection is withdrawn in view of Applicants Amendment to the claims to recite for a method of inhibiting/preventing inflammation in a host, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase (ILK) as set forth in SEQ ID NO:1.

Claims 4, 6, 7, 8, 13, 15, 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 6, 7, 8, 13, 15, 16 and 17 are indefinite because they recite the limitation "said inhibitor" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1 or claim 10, from which the claims depend recites "a compound that inhibits".

Claims 1, 4, 5-10 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting inflammation in a host *in vitro*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase (ILK) as set forth in SEQ ID NO:1, does not reasonably provide enablement for a method of inhibiting/preventing inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase (ILK) as set forth in SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 and 10 are drawn to a method of inhibiting/preventing inflammation in a host, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase (ILK) as set forth in SEQ ID NO:1. Given their broadest reasonable interpretation, the claims encompass antisense nucleic acids. The Specification at page 21, lines 33-34, page 22, lines 1-7, and Example 6, contemplates antisense nucleic acids as a compound that inhibits integrin linked kinase.

The instant specification as filed describes the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002 (see Example 13).

Wymann et al. (Trends in Pharmacological Sciences, 2003 Vol. 24:366-376) disclose that although wortmannin has been identified as an anti-inflammatory substance, wortmannin proved to be toxic to rats after given orally (see page 373, last paragraph).

The unpredictability of the art of antisense therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS, February 1998 Vol. 23, pages 45-50) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-

response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated, "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Dias et al. (European Journal of Pharmaceutics and Biopharmaceutics, 2002 Vol. 54:263-269) addresses the limitations of antisense-based therapy. Dias et al. state, "Even though the antisense strategy is widely employed currently, it has certain defined limitations. Although it is relatively easy to synthesize phosphodiester oligonucleotides, these cannot *[emphasis added]* be used as drugs due to their propensity to be easily degraded by cellular nucleases" (see page 263, first column). Dias et al. further discuss that different methods, such as electroporation, microinjection or the binding to particular peptides with membrane translocation properties have been developed to overcome internalization problems, however these methods are easily applied in cultured cells, but may or may not be useful in *in vivo* systems (see page 263, second column).

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates a method of inhibiting/preventing inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase. It is unclear how the specific the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002 data is correlated with/or representative of a method of inhibiting/preventing inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase. It is also unclear how any antisense compound that inhibits integrin-linked kinase would inhibit/prevent inflammation in a host *in vivo*, where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction for a method of inhibiting/preventing inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase. The specification does not provide guidance for the delivery of antisense compounds into the target organ and target cells in an animal in quantity sufficient to inhibit/prevent inflammation. While the specification provides guidance to the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002, the specification provides no particular nexus between a method of inhibiting/preventing inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc, for nucleic acid/antisense targeting ILK in a host *in* vivo.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002 and a method of inhibiting/preventing inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to a method of inhibiting/preventing

inflammation in a host *in vivo*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase, and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the de novo determination of how to engineer and deliver an antisense targeting ILK such that inflammation would be inhibited or prevented to any degree, particularly, in view of the obstacles needed to overcome to use antisense therapies as exemplified in the references discussed above. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to a method of inhibiting inflammation in a host *in vitro*, comprising contacting said host with an effective dose of a compound that inhibits integrin linked kinase (ILK) as set forth in SEQ ID NO:1 is proper.

Conclusion

No claims are allowable.

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PRIMARY EXAMINER